Papers and Originals

Porphyria in the Royal Houses of Stuart, Hanover, and Prussia

A Follow-up Study of George III's Illness

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[WITH SPECIAL PLATE BETWEEN PAGES 10 AND 11]

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In a previous paper based on the royal physicians' manuscript records it was proposed that George III presented the clinical picture of porphyria.[1] His illness had traditionally been called manic-depressive psychosis simply because it came in attacks during which he was excited. Essential features were ignored, foremost the physical symptoms by which they were regularly ushered in and accompanied. Nor did the diagnosis account for the fact that he was first deranged in his severest attack at the age of 50 in 1788.[2] Indeed, in contrast to the popular image, up to his 73rd year all periods of mental incapacity added together hardly amounted to six months.

Present Study

It is the purpose of the present study to establish the diagnosis of porphyria beyond doubt. Since it is hereditary we surveyed the family history for other cases,[3] and since it is a metabolic disorder we searched for a living family member in whom abnormal metabolites could be demonstrated in the laboratory. This may be considered "the material evidence"[4] of necessity missing in historical pathography, even equivalent to performing these tests on George III himself, since a coincidental occurrence of so rare a disorder may be discounted. Once porphyria has been demonstrated in only one living member, this historical study falls in line with genetic studies which trace a condition from an established propositus back to former generations.

It was not our aim to ascertain the incidence of porphyria in the House of Hanover and its blood connexions. The ramifications of the family alone would make this an impossible task, and medical records have survived for only a handful.[5] Moreover, porphyria may be latent and never cause symptoms. Inevitably many blind and inconclusive trails were followed, but, as happens in historical detection, unexpected leads also came across the centuries, as when James I told his physician that he took his attacks of colic after his mother.

Here we present clinical sketches of some historic figures in which the evidence for porphyria seemed to be most suggestive. They are not arranged chronologically but in the sequence in which discovery of one led to the next. Ultimately it was possible to trace the disorder from Mary Queen of Scots down to two living family members—through 13 generations, spanning more than 400 years (see Table I).

Porphyria in a Living Family Member

It would be sanguine to assume that because George III had 15 children it would be easy to find sufferers from the condition among his descendants—leaving aside the delicate nature of intruding into privacy in quest of specimens.

Of his six daughters, none left issue. Of his nine sons, two died in infancy. Frederick, Duke of York, died childless. Augustus, Duke of Sussex, had two morganatic children, Augustus and Ellen d'Este, who both died childless. The Prince of Wales, later George IV, had one child, Princess Charlotte, who was married to Prince Leopold of Saxe-Coburg, uncle of Queen Victoria. When she, George III's one and only grandchild in 1817, died in childbed with her infant there was no heir apparent. To remedy this calamity for the nation and the reigning house, three of his elderly sons hurriedly contracted marriages and each produced a child in 1819: Edward, Duke of Kent—Victoria; Adolphus, Duke of Cambridge—George, 2nd Duke of Cambridge; the child of the Duke of Clarence, later William IV, was stillborn. Ernest, Duke of Cumberland, also joined in the race and had a son, later the blind King George V of Hanover.

When George III died in 1820 none of his three grandchildren had completed their first year of life. In comparison Queen Victoria, who had nine children, had 27 grandchildren. His line was continued only through the Dukes of Cambridge and Cumberland, neither of whom exhibited symptoms suggestive of porphyria, and through the Duke of Kent, who appears

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[1] Macalpine, I., and Hunter, R., *Brit. med. J.*, 1966, **1**, 65–71.
[2] George III was ill in 1765 when his symptoms were physical only. But a rumour that it was his first attack of "insanity" spread after his death 55 years later and without supporting evidence came to be accepted as historical fact (Macalpine, I., and Hunter, R., *Bull. Inst. hist. Res.*, 1967, **40**, 166–85).
[3] A brief description of the last illness of George III's sister, Queen Caroline Matilda of Norway and Denmark, was given in our original paper.[1]
[4] Editorial, *Brit. med. J.*, 1966, **1**, 59.
[5] "In 1938 every ruling sovereign of Europe, with the exception of the King of the Balkan State of Albania, traces descent from Elizabeth of Bohemia [daughter of James I and great-great-great-grandmother of George III]. Their Majesties of Denmark, Great Britain, Greece, Jugo-Slavia, the Netherlands, Norway, Roumania, and Sweden are descendants of her daughter Sophia; the Kings of Belgium, Bulgaria, and Italy of her granddaughter 'Liselotte'" (Debrett's *Peerage*, 1938, Coronation Edition)—not to mention the deposed monarchs of Germany, Russia, and Spain.

to have suffered from it but not to have passed it on. Victoria's long and healthy life gives no indication of the disease and her descendants may therefore also be presumed free from it.

While it was astonishing that there was no likely sufferer in direct line from George III, there remained descendants from common ancestors. Here we report on two. In one there has been a proved attack of porphyria and in the other it was possible to establish its presence in the laboratory.

Variegate Porphyria

Knowledge of the porphyrias has steadily progressed since the studies and early classification of Günther.[6] In a classic monograph Waldenström[7] defined acute intermittent porphyria as a clinical entity, a familial disorder running a chronic course but with periodic exacerbations during which Günther's triad of abnormal pain, constipation (or diarrhoea), and vomiting become more pronounced and neurological involvement occurs. Mental symptoms are common and manifest themselves in various ways. Urinary porphobilinogen is usually grossly raised during attacks and may remain high during remissions.

A different type of porphyria, which Dean and Barnes[8] found widespread in South Africa and named variegate porphyria, runs a similar clinical course and shows the same symptoms. But in addition there is fragility and easy traumatization of the skin and/or intolerance of sunlight. Both cutaneous and abdominal-nervous symptoms may occur in the same patient, or singly in other family members. Notable features are the frequent occurrence of symptom-free cases, though "latency" is also well recognized in acute intermittent porphyria, and the greater liability of barbiturates to provoke acute attacks.

[6] Günther, H., *Dtsch. Arch. Klin. Med.*, 1912, **105**, 89; *Ergebn. allg. Path. path. Anat.*, 1922, **20**, Abt. 1, 608.
[7] Waldenström, J., *Studien über die Porphyrie. Acta med. scand.*, 1937, Suppl. 82.
[8] Dean, G., and Barnes, H. D., *S. Afr. med. J.*, 1959, **33**, 246; Dean, G., *S. Afr. med. J.*, 1960, **34**, 745.

In the laboratory it is found that during attacks patients with variegate porphyria may have moderately increased urinary porphobilinogen excretion; between attacks the faecal porphyrin is usually but not invariably above normal.[8] A more constant abnormality during the quiescent state has recently been discovered[9]: the faeces contain large amounts of porphyrin-peptide conjugates (designated X-porphyrin). Determination of this fraction is therefore of diagnostic importance.

Patient A.—A woman developed pneumonia in her sixth decade when she was attended by a distinguished physician who is a recognized authority on porphyria. He informed us that her urine was dark-red and on a number of occasions contained large amounts of coproporphyrin, uroporphyrin, and porphobilinogen. He had unhesitatingly diagnosed her as a porphyric in an acute exacerbation. Her descent from both George I and George II is shown in Table II.

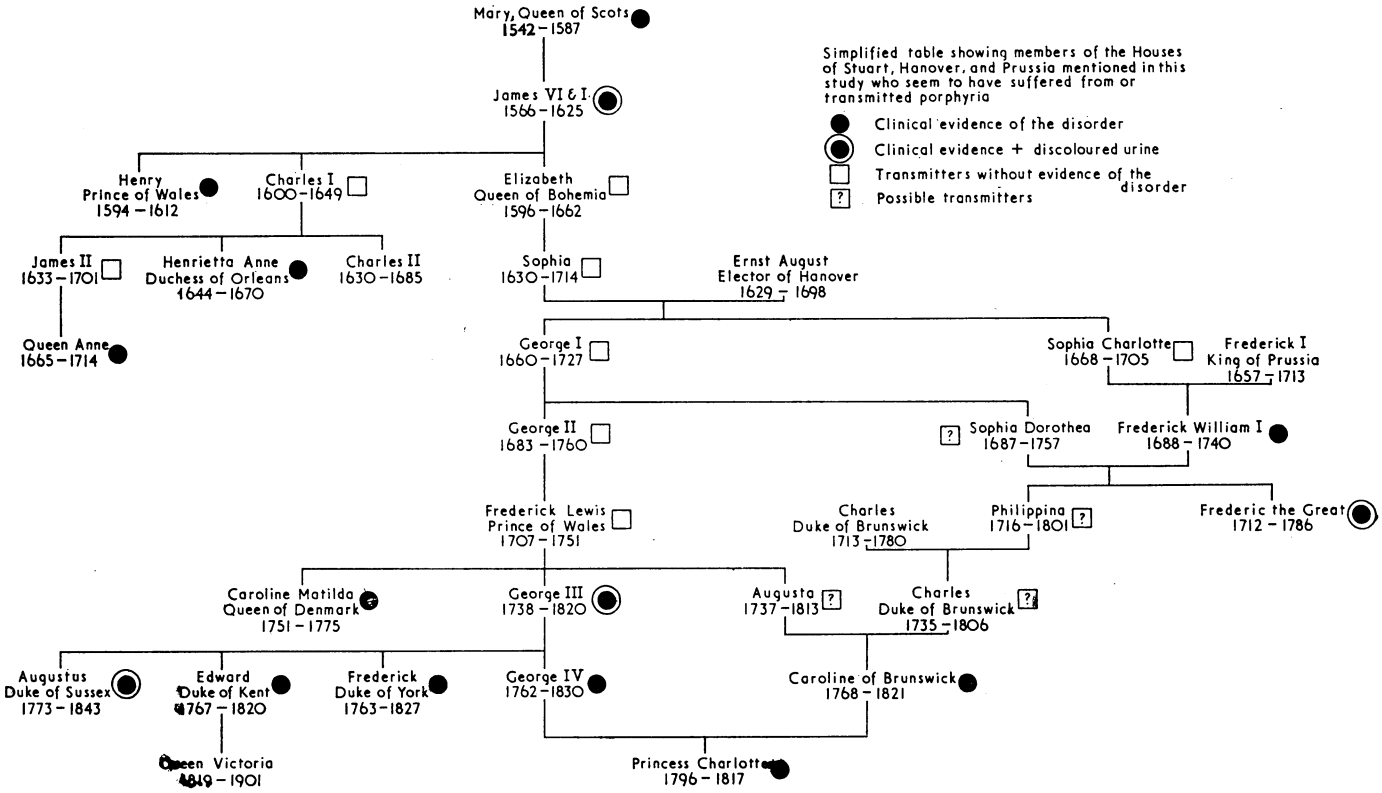
Patient B.—A woman in her fifth decade has suffered since her early twenties from attacks of colic and constipation. She described the pain as "unspeakably severe, worse than labour pains, as if one's inside were sealed off." The gastrointestinal tract had been repeatedly investigated with negative results and she had been labelled "hysterical." There was also a history of moderate sun sensitivity and easy blistering of the hands from trauma. She had learnt from experience to avoid barbiturates and sulpha drugs, which gave her headache, malaise, and pain in the limbs. Her mother had the same complaints but more severe, and she periodically passed dark, reddish urine during exacerbations. The symptoms receded in her seventh decade and eventually ceased. Her descent from George II is shown in Table II.

Laboratory Findings:

Stool	*Urine*
Coproporphyrin 13.5 μg./g. dry weight	Coproporphyrin 98.4 μg./l.
Protoporphyrin 74.0 μg./g. dry weight	Porphobilinogen 2.1 mg./l.
X-porphyrin 15.6 μg./g. dry weight	

[9] Rimington, C., Lockwood, W. H., and Belcher, R. V., unpublished.

TABLE I.—Members of the Houses of Stuart, Hanover, and Prussia who seem to have suffered from or transmitted porphyria.



Upper normal limits are difficult to define: Dean (1960)[8] states that if faecal coproporphyrin is greater than 30 and the protoporphyrin greater than 60 μg./g. dry weight, or the total porphyrins greater than 75 μg./g. dry weight, the possibility of porphyria should be considered. For X-porphyrin the upper normal value would appear to be about 8 μg./g. dry weight. Although these findings are only moderately raised, they must be taken in conjunction with the clinical history and the fact that there had been no attack for at least three years.

These findings are strong evidence that George III and affected family members suffered from variegate porphyria, since the inheritance of the various types is specific. In the isolated study of George III's illness there had appeared the picture of acute intermittent porphyria because there was little evidence that his skin was affected. As a young man he was said to have had "acne."[10] Early in the 1788 attack he had "great weals on his arms," and during attacks his face often had a violaceous hue, giving an expression of fury. In the summer of 1790 he was not well and was observed to "doze off" in the sun, so that special carriages of cane were provided to protect him. Skin sensitivity in some cases, however, may be slight and fail to impress patient or doctor; in others it may be marked, as in James I and his son. A nineteenth century family member, not included in this study, had such easily chafed skin that special uniforms were made for him ingeniously padded to avoid rubbing on neck, shoulders, elbows, and knees.[11]

Historical Method and Sources

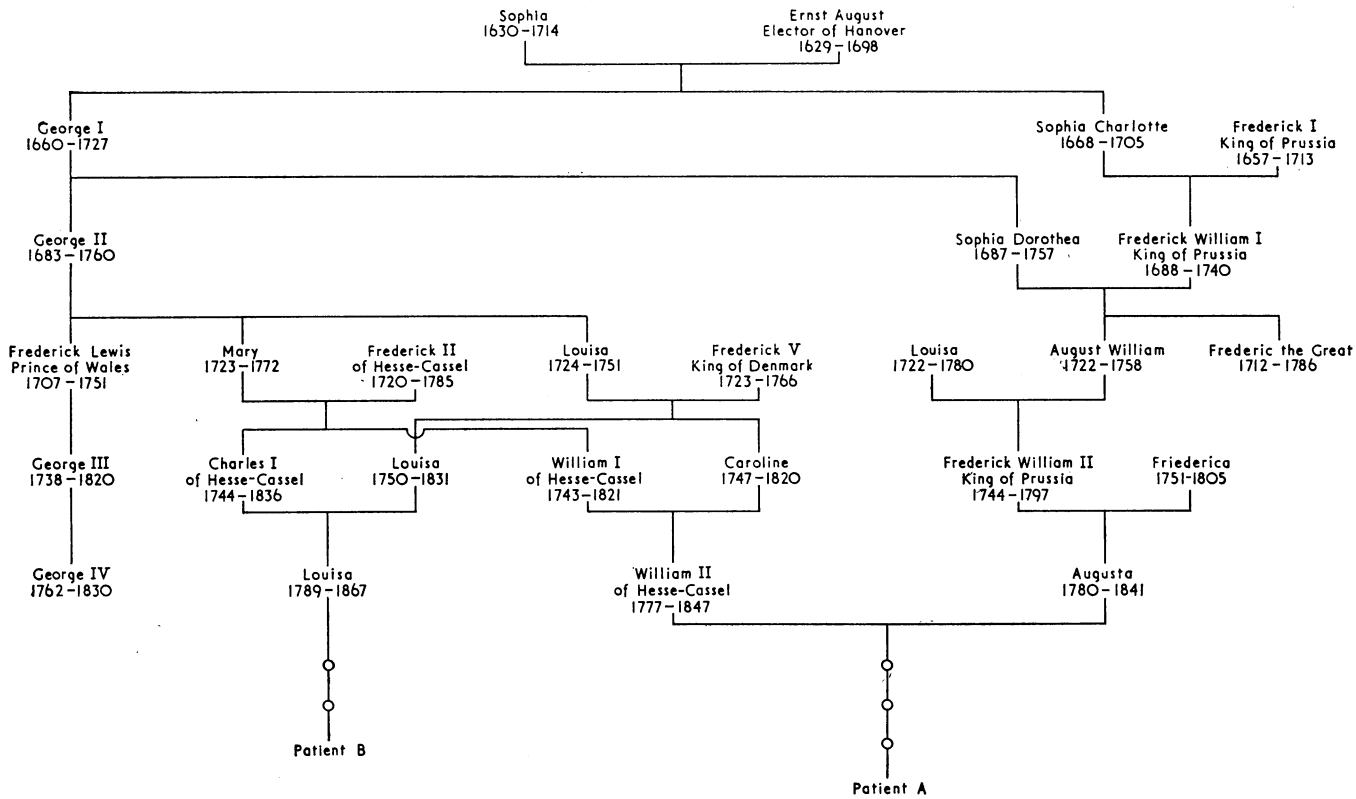
Syndrome of Porphyria

It is fortunate that porphyria can be diagnosed in retrospect with some confidence because attacks present an almost specific combination of seemingly unconnected symptoms: abdominal colic with nausea, vomiting and constipation, sometimes diarrhoea, and/or spasms localized in the chest with respiratory embarrassment; pain in the limbs, muscular weakness, transient paralyses affecting in preference extensor groups, impeding writing, standing, and walking, followed by wasting; and cerebral symptoms from depression or excitement to delirium, rigors, convulsions, and coma. Other characteristics are insomnia, fast pulse, hoarseness or loss of voice, difficulty in swallowing, transient visual impairment, headache, vasomotor disturbances, and skin lesions. Patients feel gravely ill and often have a sense of impending death. The agonizing quality of the pain is appreciated only by the sufferer, so that women tend to be considered "hysterical," as Mary Queen of Scots, and men hypersensitive, as George IV, or "impatient of pain," as James I. Rapid fluctuations occur but convalescence is protracted with great debility. Infections, even colds, can usher in an attack. It may run a fulminating course, or recur in attacks of varying, sometimes mounting severity, or peter out with advancing years. Age of onset is usually early but rarely before puberty. During attacks the urine is often coloured—from deep amber, red, or reddish-brown to purple like port wine—but this may develop only when it is left to stand and so escape notice.

Interest in urine changed in the course of medical history. After the time of the "piss-prophets," who divined everything from it, the intense curiosity in all observable natural phenomena of the early seventeenth century led James I's physician to record minute observations on his urine. In the eighteenth century this interest receded and no fresh stimulus was forthcoming from new knowledge of kidney function or disease. This explains the paradox that George III's physicians took much less notice of his urine than James I's. They had diagnosed his colics and constipation as due to gallstones and therefore watched the stools, on which they reported regularly. How little importance they attached to the urine is evident from an entry in their journal in January 1811 that the colour of the stool could not be ascertained because the urine was so deeply discoloured (British Museum Additional Willis MSS, only very recently acquired and not yet given a number).

[10] That the skin lesion of porphyria may resemble acne was remarked by Brugsch, J., *Porphyrine*, 1959, Leipzig, p. 34.
[11] Information from H.R.H. Ernst August, Prince of Hanover.

TABLE II.—Showing descent of patients A and B.



Sources of Historical Pathography

Medical facts are hard to come by. They are cavalierly treated in biographical and historical writings. Details are most likely to be found when the illness disturbed the political scene, as when George III's attack in 1788 provoked the Regency Crisis which put his physicians on their mettle, and before searching parliamentary inquiries. Similarly when the political or religious climate fostered the suspicion of poison. Porphyria with its "mysterious" symptoms—sudden onset, rapid improvement, or precipitate death, agonizing pain, vomiting, and convulsions—lent itself singularly to this interpretation, as in James I, Mary Queen of Scots, and others. So little is known of the first two Georges and of George III's father, Frederick Lewis, Prince of Wales, because their illnesses, if any, remained their private affair. Exceptionally an outstanding physician left informative notes, as Mayerne on James I, or the conscientious Hanoverian doctors on George III's son, Augustus. Often the only information is in letters, as in those of Frederic the Great and some of George III's sons. These, though laborious to find, are a safeguard against placing too much emphasis on the fatal illness, as is often done, since a porphyric need not die from the condition. Conversely, an obscure fatal illness may become clear in the light of the sufferer's earlier history. Queen Victoria's father, for example, died, it was said, of pneumonia, the result of not changing out of wet stockings—this curiously common hazard in historic figures! However his letters reveal that from his early twenties he had the tell-tale attacks of "rheumatism" and "colic."

Contemporary Diagnoses

In a medico-historical study covering four centuries one must avoid the pitfall of carrying over contemporary diagnoses literally. "Nephritis," for instance, could not have meant the same in James I's time as it does today. Then not even the circulation of the blood had been discovered and little more was known of the kidneys than that they had to do with urine and when diseased produced stones. James I's attacks of "arthritis" and his mother's "rheumatism" convey no more than that they had pain and could not move their limbs. Similar symptoms were later called "flying gout" (in contrast to podagra or settled gout) or "the ague." Distinction of fevers into tertian, quartan, and intermittent were chronological observations rather than diagnoses of malaria. Even "fever" before the clinical thermometer came into general use in the nineteenth century often indicated no more than malaise and a fast pulse. That peripheral nerves could be diseased was not recognized until late in the nineteenth century, so that paralysis of limbs was ascribed to affection of the nerves within the brain. This is why Frederic the Great's paresis at the age of 35 was called an "apoplexy" or "hemiplegia"—a diagnosis which stuck. When George IV spoke of a "stoppage" and the doctors diagnosed "an obstruction of the bowels" in his consort Caroline, it would be anachronistic to suppose they meant a mechanical obstruction of the gut as is conveyed now since the advent of *x* rays. It was rather a remnant of the old humoral pathology and implied blockage of the flow of humors causing nausea, vomiting, and constipation, much in the same sense of Mary Queen of Scots' doctors when they diagnosed "obstruction of the spleen."

Porphyria in the House of Stuart

James VI of Scotland and I of England, 1566–1625

Had King James not published a book on witchcraft[12] which entitles him to a place in the history of psychiatry we would hardly have dared so far into the past nor known where to start on George III's ancestry. As it turned out, he became the kingpin of this study. Through him it was possible to establish that porphyria came to the House of Hanover from the Stuarts. We owe the details of his medical history to Sir Theodore Turquet de Mayerne, whom he had invited from France to become his physician and who "first definitely established in England the clinical study of medicine and the method of recording observations."[13] No fitter tribute to this great physician than that his observations on James I are so complete that porphyria can be diagnosed.

Among them is a comprehensive survey of the King's health divided into descriptions of his constitution and habits and a summary of his illnesses.[14] The salient features of his disease may be gathered from a short excerpt:

"The liver . . . is liable to obstructions and generates much bile. . . . He often swells out with wind. . . . Sometimes he is melancholy from the spleen in the left hypochondrium exciting disorders . . . he becomes very irascible . . . often his eyes become yellow but it soon passes off,[15] he glows with heat, and his appetite falls off; he sleeps badly; he readily vomits and at times so violently that his face is covered with red spots for two or three days; he sometimes has difficulty in swallowing. . . . Vapours from his stomach precede illness. The alvine discharge is uncertain. . . . He sweats easily owing to his delicate skin.[16] He often suffers bruises from knocking against timber, from frequent falls, rubbing of greaves and stirrups and other external causes which he carefully scrutinizes and notes in a book to show to his physicians that it was not from an internal disorder and so avoids having to take medicines which he detests.[17] He is of exquisite sensitiveness and most impatient of pain.

"*Colic.*—Very often he laboured under painful colic from flatus (an affliction from which his mother also suffered) . . . with vomiting and diarrhoea, preceded by melancholy and nocturnal rigors.

"*Diarrhoea.*—He has been liable to diarrhoea all his life, attacks are usually ushered in by lowness of spirits, heavy breathing, dread of everything and other symptoms . . . pain in the chest, palpitation, sometimes hiccough. In 1610 his life was in acute danger with persistent vomiting. In 1612 another fit of melancholy with the same symptoms and again in 1615 and subsequent years.

"In 1619 the attack was accompanied by arthritic and nephritic pains, he lost consciousness, breathing was laboured, great fearfulness and dejection, pulse intermittent and his life was in danger for eight days.[18] A similar attack in 1623 was followed by lameness and debility.

"*Nephritis.*—He often passed urine red like Alicante wine (which are his Majesty's own words) but without attendant pain. In July 1613 blood-red urine with frequent severe vomiting, pain in the left kidney, and other nephritic symptoms. They recurred later in the year and again in 1615 even worse.

"*Arthritis.*—Many years ago he had such pain and weakness in the foot that it was left with an odd twist when walking. In 1616 pain and weakness spread to knees, shoulders, and hands, and for four months he had to stay in bed or in a chair. Three times in

[12] King James, *Daemonologie*, Edin. 1597; Lond. 1603. Hunter, R., and Macalpine, I., *Three Hundred Years of Psychiatry*, 1964, p. 47.

[13] Moore, N., *The History of the Study of Medicine in the British Isles*, Oxford, 1908, p. 116.

[14] This summary (Brit. Mus. Sloane MS 1679, ff. 42r to 51v) was printed by Moore (ibid., p. 162) in the original Latin together with a partial translation which was reprinted by Keynes, G. L., *The Life of William Harvey*, Oxford, 1966, p. 96.

[15] Exacerbations are often accompanied by transient hyperbilirubinaemia or even clinical jaundice (Gray, C. H., Rimington, C., and Thomson, S., *Quart. J. Med.*, 1948, 51, 123–37).

[16] "His skin was as soft as Taffeta Sarsnet" (Weldon, A., *The Court and Character of King James the First*, 1650, p. 165). In consequence he wore his clothes loose.

[17] James refused no medicine so decidedly as senna—George III charged Sir George Baker never again to give it to any member of the royal family and even threatened to prohibit its importation (*Diary*, quoted by permission of Sir Randle Baker Wilbraham). This may be a remarkable coincidence, but it is also possible that porphyria sufferers while their gut is paralysed cannot tolerate senna.

[18] He was so ill that "false reports" were "spread abroad of his death" from "a violent fit of the stone." He suffered intense pain, was sleepless, could not eat, lost the use of his legs for four months and had to be carried "in a Neapolitan portative chair." Later, to strengthen them "he bathes them . . in every stag and buck's belly on the place where he killed them." (*Cal. State Pap. Dom. Series*, 1619–23, pp. 32, 33, 37, 39, 56).

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PORPHYRIA IN THE ROYAL HOUSES

Ida Macalpine, Richard Hunter, and C. Rimington

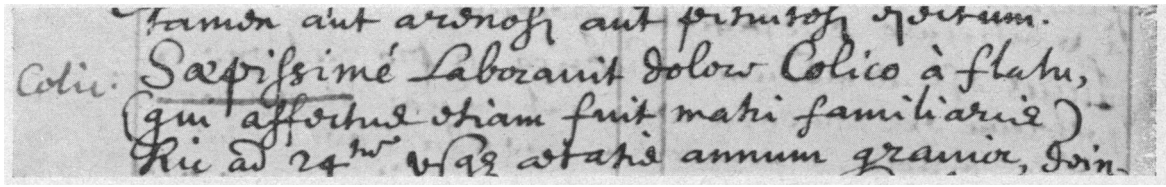
George III as Prince of Wales (pastel portrait by J. E. Liotard).

Caroline Matilda, Queen of Norway and Denmark, sister of George III (pastel portrait by Francis Cotes).

George IV, as Prince of Wales, and his consort, Caroline of Brunswick, 1797.

Commemorative medal of Princess Charlotte struck after her death in 1817.

A page from Sir Theodore Turquet de Mayerne's case notes on the illness of James I in 1613 in which he notes that the colour of the King's urine was often red like Alicante wine (British Museum Sloane MS 1679, folio 20v).



Part of a page of Sir Theodore Turquet de Mayerne's manuscript notes on James I referring to the attacks of colic of his mother, Mary Queen of Scots (British Museum Sloane MS 1679, folio 44v).

Portrait of James I's physician, Sir Theodore Turquet de Mayerne, from his posthumous book *Praxeos Mayernianae,* 1690.

Translation of text opposite (top)

12 July 1613

The King rose very early and with great vigour went riding and stag hunting until 2 in the morning. The season and the day were hot, humid and rainy. He had retention of urine. On his return he passed blood-red urine which was turbid with thick red sediment.

Then he breakfasted. After the meal he passed water again and the urine was turbid and reddish, as if lixiviated, with red sand and not at all white.

He passed his water without any pain whatever.

Shortly after he passed water a third time and it was clear.

At night nephritic pain set in from the left kidney; he vomited much and brought up phlegm which gave him relief.

He passed altogether more than six pints of thin urine clear as water with no trace of sediment as if it had been passed through a filter. The abdomen was blown out with flatus up and down.

13 July. In the morning at about 6 o'clock he felt a little better. At nine he got up and the pain in the kidney and ureter returned. The pain radiated to the bladder and the tip of the glans. Micturition was copious, the urine watery with a burning sensation at the end. He vomited phlegm with relief.

The whole of the preceding night he was feverish. In the morning the pulse was hard, febrile, unequal and missing beats as a result of the pain and restlessness.

NB About two months ago after a large meal of cherries he felt heat when making water, and often passed turbid urine as if lixiviated which was soon followed by clear urine.

NOTA This occurred without any preceding exercise; these symptoms were all nephritic.

NB His Majesty told me that since then he had quite often felt heat when passing water so that he himself feared a stone in the bladder.

He also told me that he quite frequently passed water red like Alicante wine without any pain. But not having seen this myself I cannot pass judgement on it; however most probably the water was red from blood.

Translation of text opposite (bottom)

Very often he laboured under painful colic from flatus (an affliction from which his mother also suffered).

Sophia, Electress of Hanover, from A. Halliday's *Annals of the House of Hanover,* 1826.

Mary Queen of Scots; artist unknown.

James VI of Scotland and I of England, from portrait by D. Mytens, 1621.

Queen Anne, from portrait after Kneller.

Henry, Prince of Wales, son of James I; artist unknown.

Henrietta Anne, Duchess of Orleans, Charles II's sister; artist unknown.

his life he was seized with excruciating pain in his thighs . . . which, as if by spasms of the muscles and tendons, most pertinaciously twitched at night. His legs became lean and atrophied due to lack of exercise not calling forth the spirits and nourishment to the lower limbs."

In short, King James suffered from repeated attacks of abdominal colic with nausea, vomiting, and diarrhoea, fast and at times irregular pulse, painful weakness and spasms of his limbs which early left him with a footdrop, irritability, fearful sadness, and fits of unconsciousness, accompanied by the passage of "bloody" urine, which he himself likened to his favourite port wine; and followed by prolonged weakness and debility. Once an attack began with uncontrollable weeping.[19] Mayerne diagnosed the mental symptoms as melancholy, an excess of black humor from an obstructed liver and spleen causing also the pain under the ribs and transient yellowness of the eyes. He called his painful weakness of the limbs "arthritis" because disease of joints was the only cause then known. The King's colic and gastrointestinal symptoms Mayerne attributed to "nephritis," the signs of which he described in his *Practice of Medicine*[20] as "nausea, vomiting, with a fixed pain in the loins and a deadness of the thighs." The "intention of cure" was to lubricate the urinary passages so that the stone would deliver itself and the patient from pain. Nephritis was therefore synonymous with colic and "bloody" urine proof of it.[21]

Mayerne, whose hobby was experimenting with the chemistry of pigments—a field in which he made scientific contributions—watched the colour changes of the urine with exemplary assiduity. His observations, together with more clinical detail, are contained in his day-to-day notes scattered through several volumes of his manuscripts. They have not been consulted before and are here quoted in our translation from the original Latin. From them it would appear that the urine was not discoloured by blood but most probably by the chromogens of porphyria. Mayerne himself was puzzled by some features inconsistent with haematuria due to a stone. He discussed at length where such an unorthodox stone might be situated, quoted classical authors, but—of course—found no other explanation.[22]

In June 1613 the King "was afflicted with pain in the left hypochondrium under the ribs . . . which occurred for 24 hours with mounting severity until it was worse than ferocious."[23] On 12 July (see Special Plate) on his return from hunting he passed blood-red urine. Shortly after he developed polyuria when it was colourless like water. There followed vomiting, diarrhoea, and a fast pulse with extrasystoles.[24] Mayerne waited for the pain which should accompany the passage of a stone, and as if with relief noted that "nephritic" pain did set in during the night with palpitation, diarrhoea, and insomnia, and the urine again turned red. He reasoned that a stone must have become dislodged by riding but added objectively that even without exercise the King had often and without pain passed urine purplish-brown "like Alicante wine." The next day when the King was much improved the colour of the urine was "normal enough."[25]

On 17 August 1613 he had another attack while staying at "Beaulieu Niewforest" with "tormenting pain in the left side or kidney" and "red urine." Vomiting became uncontrollable, he retained no medicine, and since he "did not admit clysters" Mayerne deliberated whether as a last resort the King should not be "immersed in a bath twice perhaps even three times." When the attack passed off, he noted that the colour of the urine returned to "laudible."[26] How serious the situation was is shown by a letter from Mayerne to Lord Rochester of 22 August in which he "Wishes four experienced physicians to be joined with himself in the charge of the King's health."[27]

Similar attacks had occurred in 1611 and 1612 with "terrifying insomnia, turbulent nights, laboured breathing, palpitation" and the appearance of "frank delirium with hallucinations" so ominous that Mayerne dreaded he was developing "water on the brain."[28] More than 175 years later George III's physicians at the height of the 1788 attack feared exactly the same and, like Mayerne, endeavoured to drive the peccant humor down again from the head into the bowels and legs "to avert the worst."[29]

Mayerne almost completed a textbook description of variegate porphyria when he added to the easy traumatization of the skin, already mentioned, the typical sensitivity to sunlight. He recorded that in the summer of 1611 the King by exposing himself to the blazing sun became so overheated that his face, especially his forehead, broke out in a vesicular rash accompanied by violent headache, vomiting, and "arthritic" pains. Neither ointment nor lotion did any good and the rash disappeared only at the end of September when the sun was less violent.[30]

The diagnosis of porphyria throws light also on James's last illness in 1625. He had one of his usual attacks and his physicians (Mayerne was absent) anticipated little danger—for which they were later reprimanded—when he suddenly took a turn for the worse, went into convulsions, and died. His death was so unexpected that Buckingham was suspected of having poisoned him by surreptitiously laying "a plaister on his stomach"[31]—testimony to the fact that as in all attacks he had abdominal pain.

And when it came to the post-mortem examination nothing much was found. The left kidney, long suspected by Mayerne to be full of mischievous stones, was healthy, and the right, of minute size, contained "two concretions," obviously a congenital, non-functioning malformation.

His doctors (and the *Dictionary of National Biography*) said he died of "a tertian fever," while medical historians have perpetuated Mayerne's diagnosis of nephritis with haematuria and arthritis, and these came later to be attributed to gout.

Henry Frederick, Prince of Wales, 1594–1612

James I's eldest son, Henry, died on 6 November 1612 at the age of 18 after a short illness with much the same symptoms which marked his father's attacks: diarrhoea, rapid pulse, insomnia, weakness, laboured breathing, violent headaches, buzzing in the ears, photophobia, rigors, muscular twitchings, mounting delirium ("alienation of braine, ravynge & idle speeches out of purpose"), fits ("all his former accidents increasing exceedinglie; his boundinges being turned into convulsions, his raving & benumminge greater; the feavor more vyolent"),[32] and finally coma. Death came so suddenly to this energetic youth of good constitution that it was rumoured he also was the victim of poison, suspicion being even cast on his father. Mayerne's daily notes on the illness have not survived. The 16 pages in his manuscript which covered it are missing, torn out supposedly by himself when opprobrium fell on him

[19] The same was reported in a doctor-patient by Dean, G., *The Porphyrias*, 1963, p. 59.
[20] *Praxeos Mayernianae*, ed. T. de Vaux, 1690, p. 349.
[21] The pain may "extend from the renal area downward to the lower abdomen, especially the bladder . . . [and] patients show the typical symptoms of nephritic colic" (Vannotti, A., *Porphyrins*, transl. C. Rimington, 1954, p. 171). "The pain sometimes radiates to the back and even the loins and bladder and is then the more likely to be mistaken for renal stones if the urine appears macroscopically bloody" (Waldenström, J., *Studien über die Porphyrie. Acta med. scand.*, Suppl. 82, p. 71).
[22] Brit. Mus. Sloane M.S. 1679, f. 21r.
[23] Ibid., f. 19r.
[24] In a series of 50 patients three had extrasystoles during attacks (Goldberg, A., and Rimington, C., *Diseases of Porphyrin Metabolism*, Springfield, 1962).
[25] Brit. Mus. Sloane MS 1679, ff. 20v, 21r.
[26] Ibid., ff. 23r, 25r, 26v, 29v.
[27] *Cal. State Pap. Dom. Series*, 1611–18, p. 198.
[28] Brit. Mus. Sloane MS 1679, f. 11r, 11v.
[29] Duke of Buckingham and Chandos, *Memoirs of the Court and Cabinets of George the Third*, 1853, vol. 2, p. 6.
[30] Brit. Mus. Sloane MS 2063, ff. 18–33.
[31] Chevers, N., *Did James the First of England die from the Effects of Poison, or from Natural Causes?* 1862.
[32] Peck, F., *Desiderata Curiosa*, 1779, vol. 1, pp. 199–204.

after the Prince died. But summary-apologias in French and Latin are included in a posthumous collection of his writings,[33] which show that the illness started on 10 October as a "tertian fever" (the same diagnosis as that made in his father's last illness), with diarrhoea, restlessness, and insomnia. He rallied for a few days but on 24 October the symptoms recurred with increasing severity. Mayerne excluded "contagious fever" because no one about the Prince was similarly affected. He noted one vitally important detail of his preceding health: in the very hot summer of the same year during the "dog-days" while staying at Woodstock with his parents and "his drinking companion Lord General Cicill [Edward Cecil]," Henry, whose favourite sport was tennis, "suffered from attacks of fever, hydroa, and inflammation of the skin of his palms and lips so severe that the whole epidermis sloughed off."[34] These lesions on the skin when subjected to trauma and sunlight are characteristic of variegate porphyria. His fatal attack had milder forerunners even earlier in that year, showing that the illness developed in the well-recognized stepladder fashion: since the spring a change had been observed in the Prince, he was "sad and retired, often complaining of a giddy heaviness in the forehead,"[35] "his countenance was not as cheerful as it was wont to be, but had heavy darkish looks, with a kind of mixture of melancholy and choler"[36] and he was often so weak and listless that he could not rise from his bed.

Prince Henry's death is generally ascribed to typhoid fever, the diagnosis put forward as the most likely by Moore in 1885[37] —long before porphyria was known—to account for the sudden onset of diarrhoea with delirium.

Mary Queen of Scots, 1542–1587

Mary Queen of Scots is one of the great invalids of history, not only the great tragic figure. Contemporaries said she suffered from the spleen, the rheum, and fits of the mother. Medical historians have refined these into gastric ulcer, rheumatism, and hysteria. From her late teens she suffered attacks of which the essential features were excruciating abdominal pain and vomiting, painful lameness, fits, and mental disturbance—a combination suggestive of porphyria. So notorious were her colics that her son who never lived with her knew of them and recognized his own affliction in hers, as he told his physician Mayerne (see Special Plate).

The most severe attack, in which she nearly died, occurred at Jedburgh in 1566 when she was 24 years old. Its rapid onset and alarming symptoms followed by quick recovery gave rise to the suspicion still lingering in some quarters that she was poisoned. She had had attacks of sickness and colic for some years, when she was suddenly taken ill, became strange in manner, nauseated, and sleepless. The next day she developed a terrible pain in her side, made worse by every movement, even breathing. She vomited continuously, it is said more than 60 times, and eventually brought up some corrupt blood. She became delirious, two days later lost her sight and speech, had a series of fits, remained unconscious for some hours, and was thought to be dead. Yet within 10 days she was up and about again.[38]

In 1570 the same symptoms recurred. She was much "molested with a continewall destillation from her head into her stomack, wherof hath growen such debilitie and weaknes in that part, that she nether hath desire to anie meate, neyther facultie to reteyne that long . . . she is troubled also with incessant provocation to vomitt . . . likewise . . . with a greit inflamation and tension in her left side, under the short ribbes which retchith so farr every waie, that they yet doubt whether it be the inflamation of the stomack, the splene, the wombe, or all of those thre partes together." She was at the same time "troubled with continual lack of sleep for 10 or 12 days (all which time she has kept her bed) . . . continually afflicted with sighs and pensiveness." She was also molested with "vehement fittes of the mother."[39]

Attacks in later years are described as "she hath complained almost this fortnight of her grief of the spleen which my physician . . . informeth me . . . is *obstructio splenis cum flatu hypochondriaco* wherewith ofttimes, by reason of great pains . . . ascending unto her head and other parts, she is ready to swoon"[40]; "complained much of grief and pain in her side, her heart, and head, and suffered then a painful fit . . . whereat she showed herself somewhat afraid of her life."[41] In 1572 she was said to have "unquiet and melancholy fits" and "sometimes grieved with passions of her old disease."[42] On one occasion her colic came upon her so suddenly on the road that she had to be taken into a house and there called for the midwife though not pregnant because the pain was so intense that she could only think of the pangs of childbirth.[43]

She herself described an attack as the "accustumat dolor of oure syde . . . ane rewme that troublis our head gritalie with a extreme pane, and discendis in the stomack, sa that it makis us lately to laik appetite,"[44] and again "vexed by sickness, with a great vomisement . . . flewme, and colore, the dolour of my syde."[45] In addition to her "shivering" and "convulsive" fits, she had difficulty in swallowing, altered voice, pain and weakness of arms and legs so that at times she could neither write, walk, nor even stand unaided, "not able to go or stand wherewith she is greatly perplexed,"[46] she "doubteth a palsy, for she says she wants strength and use of her left arm,"[47] "bereft . . . of the use of her right hand."[48] She herself wrote "excuse my writing, caused by the weakness of my arm,"[49] "the weakness . . . and the rheum wherewith we are . . . tormented,"[50] "not being suffered the command of my legs."[51]

Attacks often confined her to bed and she was melancholy, excitable, or distracted. This mental "instability" together with her recurrent invalidism and inability to move her limbs, her "grievous pain in her side," and her equally inexplicable recoveries impressed those around her as histrionic and she was believed to use illness as occasion demanded to gain her ends. Mary Queen of Scots shares with many sufferers from porphyria, living and dead, the fate of being judged "hysterical."

Henrietta Anne, Duchess of Orleans, 1644–1670, and Queen Anne, 1665–1714

Before leaving George III's ancestors two seventeenth-century Stuarts, four and five generations removed from Mary Stuart, may briefly be mentioned. They fall into the pattern

[33] Mayerne, T. T. de, *Opera Medica*, ed. J. Browne, 1700, pp. 114–6.
[34] Ibid., p. 116.
[35] Jesse, J. H., *Memoirs of the Court of England during the Reign of the Stuarts*, 1840, vol. 1, p. 168.
[36] Goodman, G., *The Court of King James the First*, ed. J. S. Brewer, 1839, vol. 1, p. 247.
[37] Moore, N., *The Illness and Death of Henry Prince of Wales in 1612: A historical case of Typhoid Fever*, 1885.
[38] Petit, J. A., *History of Mary Stuart*, transl. C. de Flandre, 1874, vol. 1, pp. 120–2; Nau, C., *The History of Mary Stuart*, ed. J. Stevenson, Edinburgh, 1883, pp. 31–2; Keith, R., *History of the Affairs of Church and State in Scotland*, Edinburgh, 1844–1850, vol. 3, p. 286.
[39] *Cal. of State Papers relating to Scotland and Mary, Queen of Scots 1547–1603*, ed. W. K. Boyd, Edinburgh, 1903, vol. 3, p. 441.
[40] Leader, J. D., *Mary Queen of Scots in Captivity*, Sheffield, 1880, p. 46.
[41] *Cal. of State Papers relating to Scotland and Mary, Queen of Scots*, op. cit., p. 3.
[42] Leader, op. cit., p. 255.
[43] Nau, op. cit., p. 15.
[44] *State Papers relating to Scotland and Mary, Queen of Scots*, op. cit., p. 435.
[45] Ibid., p. 563.
[46] *The Letter-Books of Sir Amias Poulet*, ed. J. Morris, 1874, p. 164.
[47] *Cal. of State Papers relating to Scotland and Mary, Queen of Scots*, op. cit., p. 283.
[48] Strickland, A., *Lives of the Queens of Scotland*, 1853, vol. 4, p. 412.
[49] *The Tragedy of Fotheringay*, ed. M. Scott, 1895, p. 118.
[50] Leader, op. cit., p. 163.
[51] —— op. cit., p. 537.

but the available medical details are vague and scanty, astonishingly so in the case of Queen Anne with her frequent periods of invalidism.

Henrietta Anne, youngest daughter of Charles I and sister-in-law of Louis XIV, died unexpectedly at the age of 26 after a short illness, the main features of which were excruciating abdominal pain and vomiting, rapidly followed by general muscular weakness, incontinence, respiratory embarrassment, and coma. It started on a very hot day in June when she felt "depressed and out of humor. . . . Complained many times of the pain in her side . . . said in a tone of great distress, "oh, what a stitch in my side! oh, what pain! I cannot bear it." She flushed . . . could not support herself . . . walked with difficulty . . . screamed more than ever." She had "a continual disposition to vomit" but though the pain continued "as severe as ever . . . she had not enough strength to cry." Nothing significant was found at necropsy. She had had similar milder attacks of colic, vomiting, indigestion, headache, and mood change for some years. Her brother-in-law said after her death that "above three years since, she very often complained of a pricking in her side, which forced her to lie down three or four hours together on the ground, finding no ease in any posture she placed herself in." [52]

The manner of her sudden death, age, and previous history closely resemble the fate of George III's sister, Queen Caroline Matilda, and both were rumoured to have been the victim of poison.

Queen Anne, daughter of James II, was all her life a victim to "flying gout." It was hardly ordinary gout which afflicted James I's great granddaughter cruelly from the age of 20. In her limbs it gave rise to pain and weakness so that she could not stand or walk and often had to be carried, as she was to her coronation at the age of 39. "Gout in the stomach" gave her "indigestion" and "hysterical affections"; when it went to her head it caused "the vapours," "aguish and feverish fits," rigors and convulsions; and at times her face became blotchy. In between attacks, "whenever not incapacitated by muscular infirmity occasioned by access of gout and dropsy," she was "indefatiguable" hunting the stag. She also endured, it is said, 17 unsuccessful pregnancies and the death at the age of 11 of her third and only surviving child, William Henry, Duke of Gloucester. She died in coma at the age of 49,[53] "her constitutional gout flew to the brain, and she sunk into a state of stupefaction, broken by occasional fits of delirium." [53a]

"Her life will never be justly judged," wrote a commentator, "if its sufferings are left out of account" [54] —which is as true of her as of some of her relations. It is even possible that the phrase "Queen Anne is dead" gained currency from her frequent illnesses, when "the gout vibrated fearfully through the Queen's frame from her feet to her stomach" and led to rumours that she had died.

Porphyria in the House of Hanover: George III's Descendants

George IV, 1762–1830

To turn to George III's descendants. George IV's biographers have made light of his ill-health, accusing him of "indulging" in blood letting and laudanum. But he was often dangerously ill with mysterious attacks which he took great care to conceal—contrary to the character which has been given him. He alluded to them only in strict confidence to friends[55] and on occasion even dissimulated, as when in November 1811 he excused himself from a ball because of a sprained ankle. "This took place ten days ago," wrote Fremantle to the Marquis of Buckingham, "since which he has *never been out of bed*. He complained of violent pain and spasmodic affection . . . and took laudanum every three hours . . . and lays *constantly on his stomach in bed*." [56] It was held to be "all sham" and a "want of nerves" to face his new responsibilities as Regent. But three weeks later he was still "very bad" with pain in all his limbs and "the loss of all power in them gave great apprehensions of palsy." [56]

He too was diagnosed—and is still considered—to have been a victim of gout at various sites, the first attack of which is said to have occurred in 1806 when he was 44. His correspondence however shows that from the age of 20 he had attacks of spasms in the chest, abdominal colic, pain and weakness in the limbs, insomnia, fast pulse, shattered nerves, and lowness of spirits, which left him wasted and weak.[57] "Long before . . . his thirtieth year he had been bled above a hundred times . . . the first time Dr. Warren was called in . . . [he] declared his pulse could not be counted and resembled a machine completely disorganised." [58] In 1787 "he was suddenly taken ill with an inward complaint . . . which returned so violently . . . as to keep his physicians in anxious suspense." In 1799 he wrote to his mother that he was suffering from his "old enemy, the *bile* . . . [and] was extremely indisposed with a violent bilious attack." [59] To his physician, Dr. Turton, he wrote from Bath "*Mine is a very nervous* and . . . *delicate* fibre . . . a casual cold, or even any indisposition . . . contributes much to the unhinging the whole system. . . . The waters . . . have been the means of lessening the frequency as well as the violence of my spasmodic attacks . . . which tormented me so much of late." [60] The following year he had "a violent stoppage in my bowels" with excruciating pain and "a great apprehension of impending death." [61] In 1811 when his father's attack brought about the Regency, he was also ill. The Regent, said his physician Sir Walter Farquhar, "is extremely ill . . . he suffers such agony of pain all over him it produces a degree of irritation on his nerves nearly approaching delirium. What will become of us, if, as well as our King, our Regent goes mad?" [62] He was within a year the same age as his father in 1788 when he had his first severe attack. In 1812 he had "the gout" which nearly robbed him of the use "both of my senses & my poor hand." [63] In 1813 he had again "a violent obstruction" and the next year was "so *alarmingly* ill" that Sir Henry Halford feared "another such attack would be *fatal*. It began by a spasm . . . in his bowels . . . the pain continues still very great & the pulse is high" and there was much vomiting. In 1816 he was "very weak, looks ill, is grown thinner & his legs considerably reduced, he wheels himself in a merlin chair." [64] In 1817 he described one of his attacks as consisting of "a good deal of rheumatism, as

[52] Green, M. A. E., *Lives of the Princesses of England*, 1855, vol. 6, pp 543–590, where the illness is fully documented.
[53] Strickland, A., *Lives of the Queens of England*, 1866, vol. 8.
[53a] Halliday, A., *Annals of the House of Hanover*, 1826, vol. 2, p. 547.
[54] Ward, A. W., article on Queen Anne, *Dictionary of National Biography*.

[55] For instance to the Countess of Elgin in 1799 (*Correspondence of George Prince of Wales*, ed. A. Aspinall, 1967, vol. 4, p. 41) and to Lord Liverpool in 1822 (*Letters of King George IV*, ed. A. Aspinall, 1938, vol. 2, p. 485). "How profoundly kept was the Regent's illness at least till all shadow of alarm was over," wrote his daughter in 1816 (*Letters of the Princess Charlotte*, ed. A. Aspinall, 1949, p. 244).
[56] Duke of Buckingham and Chandos, *Memoirs of the Court of England*, 1856, vol. 1, pp. 145, 162.
[57] *Correspondence of George Prince of Wales*, ed. A. Aspinall, 1963, vol. 1, pp. 53, 55, 65, 143, 149; vol. 2, pp. 163, 200.
[58] *The Historical and Posthumous Memoirs of Sir Nathaniel Wraxall*, ed. H. B. Wheatley, 1884, vol. 5, pp. 362, 363.
[59] *Correspondence of George Prince of Wales*, ed. A. Aspinall, 1967, vol. 4, pp. 44, 74.
[60] de Beer, G., and Turton, R. M., "John Turton," *Notes & Records Roy Soc. Lond.*, 1956, 12, 77–97.
[61] *Correspondence of George Prince of Wales*, ed. A. Aspinall, 1967, vol. 4, pp 132, 160.
[62] *Lord Granville Leveson Gower, Private Correspondence 1781–1821*, ed. Countess Granville, 1917, vol. 2, p. 422.
[63] *Letters of King George IV*, ed. A. Aspinall, 1938, vol. 1, p. 322.
[64] *Letters of the Princess Charlotte*, ed. A. Aspinall, 1949, pp. 86, 112, 221, 224.

much of cold, with a little touch of the bile to boot" which had rendered him "both bodily as well as mentally very unfit & indeed quite unable to take up the pen." [65]

In 1820 the disease wrought havoc in the royal House: George III died on 29 January, preceded by the Duke of Kent by less than a week. The Regent, now George IV, was too ill to attend his father's funeral. The Princess Lieven wrote to Metternich: "The King is very ill. . . . Heavens, if he should die! Shakespeare's tragedies pale before such a catastrophe! Father and Son . . . have been buried together. But two Kings!" [66] The first bulletin on 1 February stated, "The King has been attacked with an inflammation on the lungs. . . . His Majesty continues severely indisposed." His critical state so rapidly subsided that on 5 February his physicians were pleased to announce that the inflammation had not materialized! But it took him months to recover.

Attacks of "bile" and "flying gout" continued to assail him. In 1827 it severely affected particularly his left arm and both legs, but his mind remained "composed and tranquil." [66a] In 1829 there was "no appearance of stone or gravel, but violent irritation . . . only subdued by laudanum" and he "constantly talked of his brother, the Duke of York, and the similarity of their symptoms and was always comparing them." [67] The first bulletin in his last illness in 1830 mentioned once more "a bilious attack"—"an expression so vague and old-womanish" caustically commented *The Lancet*, "that nothing can be inferred from it."

Princess Charlotte Augusta of Wales, 1796–1817

Unloved and rejected by her father, separated from her mother, tossed about by her parents' discord, Princess Charlotte, daughter of George IV and only heir apparent to the throne, was not much luckier in her inherited constitution.

Married at the age of 19 in May 1816 to Prince Leopold of Saxe-Coburg, she had two miscarriages but a child was expected in October 1817. Nothing untoward was anticipated—her grandmother Queen Charlotte was at Bath, her father in Suffolk, and her mother abroad. Labour was delayed till 3 November. On the 4th her "progress" was "in every respect favourable . . . but going very slowly." At 5 p.m. on the 5th "labour . . . will, it is hoped, within a few hours, be happily completed." At 10 p.m. the delivery of a stillborn male child was announced but "Her Royal Highness is doing extremely well." Within six hours she was dead.

The nation was stunned. "It really was as if every household . . . had lost a favourite child." [68] Sir Richard Croft was accused of misconducting the confinement, and, though exonerated by the Regent, committed suicide soon after while attending a similar case. What had happened? What did she die of? Controversy, accusations, demands for an inquiry, apologias filled the papers. The facts were: after her delivery at 9 p.m. all seemed well and the physicians retired to the next room. About three hours later the nurse brought her gruel but she could not swallow, indicated acute pain in chest and abdomen, was nauseated, had tinnitus, extreme restlessness developed, respiration became laboured, she went into convulsions and expired two hours later.

The London Medical and Physical Journal thought her death unexplained: it was not due to exhaustion because many women survive similar trials; nor was there undue blood loss. It found puzzling her "almost unnatural composure not to say cheerfulness." Indeed no emotional response to her lifeless infant is recorded anywhere, an astonishing fact explicable only by her lack of insight due to already clouded consciousness. *The London Medical Repository* was equally perplexed by her sudden death and wondered whether an explanation might be found in the fact, as they had been informed, "that the whole Royal Family are liable to spasms of a violent description and to this hereditary predisposition and the increased excitability of the amiable Sufferer are we left to ascribe an event which has destroyed the flattering hopes of a nation." On the centenary of her death *The Lancet* reopened the case and raised but rejected the theory that it was due to pulmonary embolism. A correspondent judiciously pointed out that the post-mortem examination had revealed not only "loss of uterine tone" but "general atony of the viscera," as shown by a distended colon and dilated stomach which contained three pints of fluid.[69] In 1951 Eardley Holland once more received this "triple tragedy" but still could offer no satisfactory obstetric explanation. He concluded that it "is unlikely that there will ever be more exact data for finality." [70]

Her delayed and protracted labour and death appear in fresh light when her medical history is taken into account. From the age of 16 she had frequent attacks of abdominal pain, severe headache, insomnia, loss of appetite, and a fast pulse, which left her "quite fagged & blown out" and "a good deal pulled down." She was often depressed, "horribly and detestably out of spirits" or excited and excitable. Curiously, at such times she talked too fast—a prominent feature in George III's attacks. She wrote: "Last night I had a slight *nervous* attack again which always affects my spirits as well as my side. . . . I feel . . . oppressed as if my heart would burst or sigh itself out . . . like suffocation my breath feels so heavy." These episodes were considered sufficiently serious to bleed and blister her and apply leeches, "a nasty opperation." [71] Sir Henry Halford told her father when she was 17 that "The Princess has for some time but more lately complained of a pain in her left side," but because she had no difficulty lying on either side and her skin was not hot he diagnosed it as "only muscular." [72] However since her pulse was fast and she was "low and nervous" he put her on a restricted diet. Dr. Matthew Baillie thought the pain due to distension of the stomach and constriction in the chest.[73] Her governess found her "much thinner, as she had been reduced by the medicines she had been obliged to take for a pain in her side, occasioned by a bilious disorder, which was erroneously treated as nervous." [74] She herself wrote: "I am in a terrible bad state of nerves, spirits . . . & such a nervous headache that I can scarcely open my eyes." [75] And to her father she wrote the following year of her "bilious complaints (which I am sorry I am but too liable to)." [76] During her pregnancy she was repeatedly "indisposed," "occasionally suffered . . . from headache," was bled and kept on a "low" diet without meat to subdue "her morbid excess of animal spirits." [77]

Today 150 years almost to the day after this sad and enigmatic event the mystery may be resolved. Cases have been observed where a fulminating attack of porphyria set in a few hours after confinement with restlessness, cerebral irritation, difficulty in swallowing, other signs of bulbar involvement, and finally respiratory paralysis.[78] Charlotte could have inherited porphyria from her father. But since her parents were first cousins and her mother possibly also affected, her risk may have been even greater.

[65] *Letters of King George IV*, ed. A. Aspinall, 1938, vol. 2, p. 223.
[66] *The private letters of Princess Lieven to Prince Metternich*, ed. P. Quennell, 1937, p. 11.
[66a] Sir Robert Peel to Sir Henry Halford (February 1827). Halford Papers.
[67] *The Greville Diary*, ed. P. W. Wilson, 1927, vol. 1, p. 121.
[68] *Memoirs of the Life and Time of Henry Lord Brougham by Himself*, 1871, vol. 2, p. 332.
[69] Morison, A., *Lancet*, 1917, 2, 874.
[70] Holland, Eardley, "The Princess Charlotte of Wales: A triple tragedy," *J. Obst. Gyn. Brit. Emp.*, 1951, 58, 905.
[71] *Letters of the Princess Charlotte*, ed. A. Aspinall, 1949, pp. 43, 52, 160, 169.
[72] *Letters of King George IV*, ed. A. Aspinall, 1938, vol. 1, p. 285.
[73] Ibid., p. 496/7.
[74] *Autobiography of Miss Cornelia Knight*, 1861, vol. 2, p. 78.
[75] *Letters of the Princess Charlotte*, ed. A. Aspinall, 1949, p. 190.
[76] *Letters of King George IV*, ed. A. Aspinall, 1938, vol. 2, p. 78.
[77] Huish, R., *Memoirs of Charlotte Augusta Princess of Wales*, 1818, p. 514.
[78] Goldberg, A., personal communication.

Caroline of Brunswick, Queen Consort of George IV, 1768–1821

Unfortunately little is known of Charlotte's mother's medical history other than that she had episodes of ill health and "was afflicted with violent rheumatic pains and by severe spasmodic attacks" while living abroad.[79] She was often melancholic and at times bizarre, as when she founded at Jerusalem the Order of St. Caroline and created her friends grandmaster and knights thereof.[80] Her fatal illness at 53 started immediately after her greatest humiliation when the guards barred her entry to Westminster Abbey for the coronation of her husband on 19 July 1821. *The Times* had "no doubt that the Queen died of a broken heart . . . [and] suppressed grief."

She had been ill several days with colic, constipation, and a fast pulse,[81] when a bulletin announced that Her Majesty had "an obstruction of the bowels." Pain and suffering were intense, she vomited violently, was restless and excited, respiration became difficult, she became delirious, rallied for a short time, but died in convulsions on 7 August. The possibility of porphyria is strengthened by her inheritance[82]: her mother Augusta, George III's sister, had married her second cousin, Charles William Ferdinand, Duke of Brunswick. He, like the Georges, descended from the Electress Sophia through his mother Philippina, daughter of Frederick William I, King of Prussia (see Table I). Caroline could therefore have inherited the disorder from either or both parents. But was there any evidence of porphyria in the Brandenburg-Prussian House? A glance at the genealogical table suggested that Frederic the Great was the obvious figure to investigate.

Porphyria in the House of Prussia

Frederic II, called The Great, King of Prussia, 1712–1786

Proverbially the monarch on crutches, victim of gout and indigestion, Frederic the Great is also the one about whom most was written. When in the 1850s Carlyle wrote his six-volume biography he complained that the literature on Frederic the Great already amounted to "wagon-loads." Yet his medical history is poorly documented—he changed his doctors too often for any one to have an overall picture. Drs. Selle and von Zimmermann who attended parts of his last illness published accounts of it, but neither is sufficiently informative to allow a modern diagnosis. Of his past Selle only mentioned that "In his early years the King suffered from a peculiar debility and sensitiveness of his stomach with much vomiting, attacks of colic and obstruction of the bowels . . . from his 28th year he had attacks of gout . . . at 35 he was attacked by a hemiplegia which however quickly yielded to antiphlogistic treatment"[83]—in other words was transient. Zimmermann described the exquisite severity of the pain and related how "When the gout racked his whole body he named the sites of the most excruciating pain after the English Opposition; he used to say 'Mr. Burke is busy in my knees and Mr. Fox in my feet.'"[84]

Frederic's extensive correspondence reveals that in 1732, when not yet 20, he had "horrible headaches, migraine, an upset stomach,"[85] had hoped to recover more quickly but continued "at war" with his stomach and had "lost a terrible amount of weight during the attack." At 24 "migraine is epidemic" with him, he suffers from headache, is so weak that "it needs a mere bagatelle to throw us over, and a nothing to destroy us," and so melancholic that "We can glory in nothing but our miseries." At 25 he had to take medicines "to cure my abysmal stomach . . . what does it matter, we must die some time whether of gout, gravel, the King's evil or colic." At 34 "An obstruction . . . has turned into gout . . . my severe headache threatens to paralyse my right arm, and gravel my left." At 35 he had one of his worst attacks and what his

Frederic II, King of Prussia, aged 73, from Cunningham's engraved picture of what is called "Frederic's Last Review."

doctors called a "hemiplegia"—and posterity accepted literally. To Voltaire he described it less misleadingly nine days after its onset when it had already subsided as an "incomplete apoplexy."[86] How ill he felt he told a friend: "Once again I have escaped from Pluto's realm, but I was only one station away from the Styx and heard Cerberus howl"[87]—"I have most wonderfully escaped the jaws of death," wrote George III to Bishop Hurd after his attack of 1801.

Medically the most informative are Frederic's uninhibited letters to his valet whom Voltaire called his "old factotum."[88] To him Frederic confided in 1745 aged 33, "My health has suffered considerably [from the hardships of the campaign]. I cannot sleep at night because of palpitation, cramp and colic." A little later his "chief complaint" was being "still constipated like a Turk." Three weeks after his "hemiplegia" he wrote "my doctor is an optimist if he really believes that strokes and renal colics are nature's way of restoring health [by eliminating peccant humors]; I speak from bitter experience being so weak that the smallest exertion bowls me over." He also had pain "in the spleen and kidney" but whether through "an obstruction or a tumor" he did not know. The colic was "under the ribs radiating to the back," he suffered severe cramp, vomited much, had pain in the arms "as if paralysed." A month after the onset he foamed in desperation, "The whole illness, the physicians have now at last discovered, is the result

[79] Huish, R., *Memoirs of Queen Caroline*, 1825, pp. 31, 41, 52.
[80] Greenwood, A. D., *The Hanoverian Queens of England*, 1911, vol. 2, p. 332.
[81] *Annual Register*, 1821, vol. 63, pp. 118–9.
[82] There was much illness in this "middle" branch of the Brunswick line and it died out in the 1880s.
[83] Selle, C. G., *Krankheitsgeschichte des höchstseligen Königs von Preussen Friedrich des Zweyten Majestät*, 1786, p. 5.
[84] von Zimmermann, J. G., *Fragmente über Friedrich den Grossen zur Geschichte seines Lebens, Leipzig*, 1790, vol. 3, p. 18.
[85] This and the following quotations are from: *Briefwechsel Friedrich's des Grosen mit Grumbkow und Maupertuis*, ed. R. Koser, Leipzig, 1898 (Publ. aus dem K. Preussischen Staatsarchiven, vol. 72 [in French]), pp. 13, 15, 135, 149.
[86] Frédéric to Voltaire, 22 February 1747 in *Oeuvres de Frédéric le Grand*, ed. J. D. E. Preuss, Berlin, 1853, vol. 22, pp. 163–5.
[87] *Die Briefe Friedrichs des Grossen an seinen vormaligen Kammerdiener Fredersdorf*, ed. J. Richter, Berlin, 1926, p. 96.
[88] This and the following quotations are from ibid., pp. 75, 77, 85, 95–100, 112, 114, 116, 140, 373.

of a kidney disease, after they have tortured my colon for four weeks like a pack of hounds." What else, one may wonder, could possibly have made his doctors suddenly so certain that his kidneys were diseased but having observed "bloody" urine. Colic, constipation, pain in the limbs and weakness, and insomnia persisted for more than two months and convalescence was slow.

Attacks recurred throughout his life. In 1755 he consoled his valet, who was also ill: "You can't piss, and I can't walk." To Voltaire he wrote in 1758 of his "nephritic colics" and in 1779 that he was "just coming out of my 14th attack of gout which has tormented me cruelly [and] robbed me of the use of my limbs."[89] He visited spas regularly and was bled as a precaution four times a year. Between attacks he was capable of great exertions and enduring physical hardships.

Frederick William I, King of Prussia, 1688–1740

Frederic the Great could have inherited porphyria from either parent, since they were first cousins descended from the Electress Sophia. His father first had "nephritic colics" at the age of 31 in an attack which brought him to the brink of death. At 39 he had violent attacks of gout; his temper became uncontrollable, he was sleepless, and "worried himself into melancholy and hypochondria," had "a fit of religious mania" and spoke of abdicating.[90] In 1729, aged 41, he had his most serious attack with colic, insomnia, painful weakness of his limbs, and had to be wheeled about. To distract himself from his sufferings he painted and signed the pictures *Friedericus Wilhelminus in tormentis pinxit*.[91]

Porphyria among George III's other Sons

Dr. von Zimmermann, physician to George III in Hanover, and of international repute, is an extraordinary link between the royal porphyrics of Prussia and England. To him as royal physician the Hanoverian Privy Council turned when news reached them in November 1788 of George III's serious illness.[92] He replied: "How can I advise on the distressing and highly dangerous illness of our most gracious sovereign when I have not enough information even to form an opinion on the nature of the illness! Nothing can be gathered from the news which reaches us from London. It is impossible—and would not be justified—to rely on the English newspapers which are so often full of lies .... No doctor on earth could divine the nature of the illness without knowing the facts—still less suggest treatment. From the first dispatches it sounded like an apoplexy, but today they mention an acute delirium .... But not a single symptom is described which enables one to decide whether it is an inflammatory, a bilious or a putrid fever ... or whether perhaps some gouty matter, or even water has settled on the brain and produced these threatening symptoms."[93] They ordered him to the Hague for easier access to London both for receiving news and in case he should be summoned to the King's bedside. But not a word reached him from his English colleagues. "I implore you fervently," he wrote to the councillors at Hanover, "to persuade at least one of the Royal Physicians to send me a detailed, frank, professional report on how the illness developed." On 5 December—the very day the Reverend Dr. Francis Willis took charge of the royal sickroom at Kew Palace—he complained bitterly of having been exposed to this fruitless and hazardous trip into snowbound Holland: "I knew from the outset that the purpose of the Privy Councillors ... would never be fulfilled, even if the honourable gentlemen themselves did not realize that the English physicians would in no circumstances whatsoever permit me to have only the slightest share in the King's treatment." Exhausted and outraged, he returned to Hanover.

Frederick, Duke of York, 1763–1827

"I think it my duty to acquaint you, Sir," wrote George III's second son, Frederick, in June 1786 to his father from Hanover, "that ... I had a letter from the King of Prussia in which he begs me to send Dr. Zimmermann to Potsdam."[94] He himself had been Zimmermann's patient in 1783 when he was seriously ill at the age of 20 and Zimmermann had sent full reports to his father. The following summer he had "a feverish cold ... of the aguish kind" caused by "the excessive heat of the weather."[95] In 1785 when he was 22 Zimmermann sent him to Pyrmont Spa "as the only thing which would thoroughly cure me of the terrible cramps and spasms in my stomach, to which I have been very subject for the last two years."[96] In July 1789 in London he developed "a very large eruption all over his countenance," which Dr. Warren thought was measles, followed by "a complaint in his bowels" and "tightness on breast" so severe that he was bled and had to take laudanum.[97] In September the same year he was attacked by a "very violent intermitting fever which ... has reduced me so exceedingly low that it will require a considerable time for me to recover."[98] In June 1796 he "was so exceedingly unwell all day yesterday, and though perfectly free from spasm today, yet so exceedingly weak," and his brother found him "extremely ill indeed, and hardly able to speak."[99] In July *The Times* reported that he had a return of his "stomach complaint." In 1820 George IV wrote to him: "It grieves me much to learn that you have been indispos'd. ... You talk of an attack of bile; I also have had my share of it ... and my old enemy the gout flying about me."[100] He was seriously ill again in 1823 and died of "dropsy" in 1827.

Augustus, Duke of Sussex, 1773–1843

Augustus, George III's sixth son, was like his brother, Frederick, also Zimmermann's patient while living at Hanover and Göttingen. We owe to him and his three colleagues in attendance on the Prince, Drs. Stromeyer, Richter, and Fischer, a most informative account of a series of dangerous illnesses which befell Augustus when he was still in his teens.[101]

It started in August 1788 when he was 15 with "fearful paroxysms," which they described in great detail: spasmodic constriction in the chest with reddish-brown discoloration of the face not unlike convulsive asthma but with exquisite pain, restlessness, and anxiety; insomnia, nocturnal excitement, giddiness, severe headaches; extreme languor and general weakness. These paroxysms became so violent that there was immediate danger he might suffocate. They noted the colour of the urine "changed repeatedly" during the illness: "at times it was very pale, at others deeply coloured"; during exacerba-

[89] Frédéric to Voltaire, 6 October 1758 and 4 December 1775 in *Oeuvres*, vol. 23, pp. 21, 358.
[90] *Wilhelmina Margravine of Baireuth*, ed. E. Cuthell, 1905, vol. 1, pp. 63, 80, 184.
[91] Carlyle, T., *History of Friedrich II of Prussia, called Frederick the Great*, 1858, vol. 2, pp. 53–5.
[92] The material relating to Dr. von Zimmermann is in Niedersächsische Staatsarchiv Hanover, Han. Des. 92 III B No. 5.
[93] This report which reached Hanover from London is of interest because it confirms that George III became delirious in the train of physical disease.
[94] *Later Correspondence of George III*, ed. A. Aspinall, 1962, vol. 1, p. 232.
[95] Ibid., p. 74.
[96] Ibid., p. 162.
[97] Ibid., p. 429.
[98] Ibid., p. 441.
[99] *Correspondence of George Prince of Wales*, ed. A. Aspinall, 1963, vol. 3, p. 231; *Later Correspondence of George III*, vol. 2, p. 492.
[100] *Letters of King George IV*, ed. A. Aspinall, 1938, vol. 2, p. 370.
[101] The following information about Prince Augustus and the Duke of York is in Niedersächsische Staatsarchiv, Hanover, KG Hann 9 Domestica No. 147 and Hann 92 Domestica No. 147c.

tions it was "deep amber" or "reddish" and in remission "the colour returned to normal."

Zimmermann reported to George III that they did not know what this highly complicated illness was but it resembled his brother Frederick's attacks in 1783. He referred the King for details to the regular reports and full consultation he had sent to their Majesties at that time,[102] as the condition of Augustus was now exactly the same. There had been four previous paroxysms. About the nature and prognosis of the illness the physicians concluded: "in respect of the likelihood of recurrences we believe His Royal Highness has a peculiar disposition to paroxysms of a violent kind, but in what this disposition consists we cannot determine[103] . . . it may be the result of some bodily irritation which settles on the chest. We are however agreed that there is no ulceration in the lungs[104] . . . It has come to our knowledge that several members of the Royal Family and in particular His Royal Highness the Duke of York and Prince Edward [Duke of Kent] are subject to the same paroxysms and this arouses our suspicion of a hereditary predisposition."

Augustus had many more such spells. In 1790 he himself described a near fatal one to his father: "Such a painful and long illness I have not yet had. Seven times blooded, two blisters . . . Such a day as . . . Friday was dreadful, so just between life and death, all my faculties for a good four hours so entirely gone, that what passed that time I am quite ignorant of . . . I am weak, Sir, and cannot write more."[105] From 1800 his attacks diminished and appear to have ceased after 1817.[106]

Edward, Duke of Kent, 1767–1820

Although George III's sons recognized the similarity of their complaints, we have been able to find only one who knew, or perhaps dared to admit, that his and his father's symptoms were identical. Edward, Duke of Kent, was 23 when he wrote in 1790 to George III—whose illness in 1788–9 had started with colic, diagnosed as biliary concretions in the gallduct—"my health has so materially suffered during the immoderate heat of last summer that the Surgeon General of our Garrison, who has constantly attended me during the frequent bilious attacks from which I have felt the most violent and serious effects, has given it as his positive opinion that by my remaining here [Gibraltar] another summer season my health would be exposed not only to the most prejudicial but perhaps the most fatal attacks of a complaint, the severity of which, is, I believe, not unknown to your Majesty."[107] Attacks of pain and weakness in his limbs had occurred even earlier: in 1788 he was recovering from "a violent rheumatism . . . which nearly deprived me of the total use of both my hands."[108] "Violent bilious attacks"[109] recurred and in Halifax, Nova Scotia, he "had one of the severest bilious attacks . . . ever . . . and . . . a very violent rheumatism settled in my head for several days."[110] His skin was also affected: in the spring of 1800, aged 33, he complained of "being unable for 6 weeks to wear anything but a pair of loose trowsers from a troublesome humor which, after shewing itself in several parts of my body, at length settled in my legs; indeed at this moment one of my eyes is nearly closed from the same cause."[111]

His short fatal illness in 1820, attributed to pneumonia, was more like an attack of porphyria ushered in by an infection, with hoarseness, embarrassed respiration, hiccough, and delirium. That he was not free from abdominal pain during the last year of his life may be gathered from an anecdote which records that he was so sympathetic to pain in others that while his wife was carrying Victoria he developed symptoms of the "*couvade*"![112]

Summary and Conclusions

It was the purpose of this follow-up study of George's III's illness to raise the diagnosis of porphyria previously made above the uncertainties inherent in posthumous pathography.

This was achieved when a living family member was found suffering from it and when in another it was possible to demonstrate the biochemical abnormalities of variegate porphyria by the latest laboratory techniques.

Armed with this knowledge we searched George III's descendants and ancestry for other cases. Evidence is adduced which suggests that four of his sons and his granddaughter, Princess Charlotte, suffered from it.

Among his ancestors and collaterals, through the fortunate survival of informative medical records, the disorder could be traced back to Mary Queen of Scots and her son, James VI of Scotland and I of England. Most remarkable, of him even the repeated passing of the typical port-wine-coloured urine is recorded which he likened to his favourite Alicante wine, still obtainable today. His son, Henry, Prince of Wales, appears to have died in an attack at the age of 18. From James I it must have been transmitted through his daughter, Elizabeth, Queen of Bohemia, to her daughter Sophia, wife of Ernst August, Elector of Hanover. From her, foundress of the English House of Hanover, it must have come down through her son George I to George III and his descendants; and through her daughter, Sophia Charlotte, wife of Frederick I, King of Prussia, in the Brandenburg-Prussian line to Frederic the Great, cousin-german to George III.

The clinical data yet to be gathered from study of this uniquely documented family—spanning 13 generations and more than 400 years—may well add to knowledge of this rare and still incompletely understood disorder. Its dramatic and mysterious features gave rise on five occasions to the suspicion of foul play and created a *cause célèbre*: the illness of Mary Queen of Scots in 1566; and the deaths of the Prince of Wales in 1612, of James I in 1625, of Henrietta Anne, Duchess of Orleans, sister of Charles II and sister-in-law of Louis XIV, in 1670, and of Caroline Matilda, hapless Queen of Denmark and Norway, sister of George III, in 1775.

The character of some historic figures may now appear in a somewhat different light when their sufferings are seen to have been real and severe, as in the case of Mary Queen of Scots and George IV. Foremost the traditional image of George III, distorted by the false assumption that his illnesses were psychological breakdowns, urgently needs to be looked at afresh.

Porphyria may justly be called a royal malady. It caused directly two major national disasters: the Regency Crisis in 1788 when George III had his severest attack, and the catastrophe of 1817 when Princess Charlotte died in childbed with her infant. This tragedy threatened the Hanoverian succession with extinction and left the nation without an heir apparent until the birth in 1819 of Victoria. Porphyria may also have contributed to Queen Anne leaving no heir, a calamity which necessitated

[102] Unfortunately these reports could not be traced.
[103] To the parliamentary inquiry into George III's health in December 1810 Dr. William Heberden deposed about the nature of his illness: "It is a peculiarity of constitution, of which I can give no distinct account."
[104] When George III was ill in 1762 and 1765 he also had predominantly chest pain with embarrassed respiration which led to fears that he was developing "a consumption" (*see* footnote [3]). Angina-like pain is known sometimes to usher in attacks (Waldenström, J., *Studien über die Porphyrie, Acta med. Scand.*, 1937, Suppl. 82, p. 73).
[105] *Later Correspondence of George III*, ed. A. Aspinall, vol. 1, p. 493.
[106] Fulford, R., *Royal Dukes*, 1933, p. 277.
[107] *Later Correspondence of George III*, vol. 1, p. 507.
[108] Ibid., p. 382.
[109] *Correspondence of George Prince of Wales*, ed. A. Aspinall, 1964, vol. 2, p. 137.
[110] *Later Correspondence of George III*, ed. A. Aspinall, 1967, vol. 3, p. 380.
[111] *Correspondence of George Prince of Wales*, ed. A. Aspinall, 1967, vol. 4, p. 124.
[112] Stuart, D. M., *The Mother of Victoria*, 1941, p. 76.

safeguarding the Protestant succession by the Act of Settlement of 1701, by which the crown was transferred from the Catholic House of Stuart to that of Hanover, and so brought George I and his descendants to the English throne.

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The portraits of Mary Queen of Scots, James I, Henry, Prince of Wales, Queen Anne, Henrietta Anne, Duchess of Orleans, and George III are reproduced by permission of the Trustees of the National Portrait Gallery, and that of Queen Caroline Matilda by permission of the Courtauld Institute of Art. We also thank the Trustees of the British Museum for permission to reproduce two pages from Mayerne's manuscripts.

Endolymphatic Therapy for Malignant Melanoma

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Among those who have studied malignant melanoma there is general agreement that the primary tumour should be widely excised to prevent local recurrence. It is also agreed that regional lymph nodes should be excised if on clinical examination they seem to be involved. Where uncertainty and disagreement occur is in the management of patients in whom the regional nodes are clinically uninvolved. Fortner *et al.* (1964), who performed routine block dissections in such patients, found that in 38% of them the nodes contained microscopic metastases. Block dissection, inevitably and unfortunately, carries definite morbidity and mortality rates, and many surgeons prefer to avoid its routine use, waiting to see if nodes become enlarged before operating.

Endolymphatic therapy to nodes in such cases is largely free of the complications and disadvantages of block dissection. Earlier work (Edwards *et al.*, 1965, 1966; Edwards, 1966) has suggested that it might be effective in place of block dissection. Where the metastases are microscopic they might be destroyed, and over a greater anatomical range than by block dissection; and where there are no secondaries no harm would be done. We have used it routinely after excision of primary melanomas, as the sole initial treatment to the regional nodes when they were not enlarged, or after a suitable interval followed by block dissection if they appeared to be involved. The treatment is described in greater detail below.

Endolymphatic therapy consists of an injection into a lymph vessel near the primary site so that the lymph pathways, the vessels, and nodes draining the tumour area are filled. The material injected, usually a radioactive isotope, lodges in the nodes, where it delivers a heavy dose in close proximity to metastases should they exist. When the isotope is, for example, iodine in Lipiodol the nodes are opacified and radiographs may reveal metastases that might be undetected clinically. Further changes in nodes may be studied in subsequent radiographs, as the medium remains in the nodes for several months.

We report here observations on a group of patients given endolymphatic therapy and compare them with another group treated without its use.

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Clinical Staging and Management of Melanoma

Clinical staging of melanoma (stage I, primary alone; stage II, regional nodes involved, analogous to that used for carcinoma of the breast) has proved useful in prognosis and treatment, though other authors have not, so far as we can find, made use of it to any extent.

Clinical stage I melanoma is defined as primary melanoma with the regional nodes clinically negative, and clinical stage II melanoma as primary melanoma with the regional nodes clinically positive.

Treatment of Primary Lesion in Clinical Stage I Melanoma

Role of Biopsy.—Where the diagnosis of melanoma is highly probable on clinical grounds full definitive excision is performed without previous biopsy. Otherwise suspicious lesions are first excised with a clear margin of apparently healthy skin around the mole and further treatment given when indicated. Incisional biopsy—that is, actually cutting out parts of the tumour—is avoided.

Definitive Treatment of Primary Melanoma.—Many of the patients had primary melanoma situated on the lower limb. The description below relates largely to this site. The excision is wide in extent and a skin graft is necessary to cover the defect unless an amputation is done. The excision should be sufficient to exclude recurrence due to intradermal lymphatic permeation. This usually means excising an ellipse of skin some 6 by 4 in. (15 by 10 cm.) with its long axis in line with that of the limb. The depth of excision included the deep fascia in nearly all our earlier cases when the primary was treated in our own clinic. More recently we have taken the excision down to the deep fascia but left this layer intact following Olsen's (1964) report suggesting that this made recurrence less likely.

In most instances the lesion and surrounding skin have been gently washed with surgical spirit and covered with a layer of Nobecutane or Steridrape before excision. After complete excision the operation area is washed with clorpactin or distilled water to kill loose cells. The skin graft has always been taken from the opposite limb as a first separate operation in order to avoid possible contamination and implantation of tumour cells.